Rejection Under 35 U.S.C. § 112, first paragraph

Claims 6-14 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied in view of the attached Declaration submitted under 37 C.F.R. § 1.132.

The Examiner has stated that the specification, while being enabling for *in vitro* site directed mutagenesis of a target DNA, or site directed mutagenesis of a target DNA molecule *ex vivo* in cultured or isolated cells, does not reasonably provide enablement for *in vivo* methods of site directed mutagenesis of a target DNA molecule. The Declaration submitted herewith, under 37 C.F.R. § 1.132, provides conclusive evidence that specific triplex forming oligonucleotides (TFOs) bind to targeted genomic sites and induce mutations *in vivo* (i.e. oligonucleotide-specific induction of mutagenesis in mice). The applicants have demonstrated the induction of mutagenesis in a variety of tissues with a triplex forming oligonucleotide (AG30) designed to bind to the chromosomal triplex target site in transgenic animals. The accompanying Declaration clearly demonstrates the successful application of a site-specific, DNA binding reagent that specifically induces genome modifications on a chromosomal target in intact animals.

In specific regard to issues raised in the Office Action mailed on August 15, 2002, relating to the quantity of experimentation that would be required to achieve the claimed technology *in vivo*, and the delivery and penetration of triplex forming oligonucleotides into tissues of intact animals, the Applicants have provided studies demonstrating the substantial uptake in a number of tissues except for the brain (brain tissue mutagenesis measured as an

internal control because of the blood brain barrier). As evident from Table 1, the average mutation frequencies in liver, kidney, skin, colon, small intestine, and lung, as a result of the triplex forming oligonucleotide binding to the polypurine site in *supFG1* (AG30), were significantly higher than tissues derived from the control treated mice. Furthermore, the Applicants have eliminated the idea that the induced mutagenesis obtained from the AG30 treated animals may have resulted from a non-specific effect. This is based upon a lambda cII gene mutation reporter that showed no induction of mutagenesis in animals treated with either AG30 or the negative control oligonucleotide (SCR30) as compared with background levels (see Table 2). These results are consistent with a gene-specific, triplex mediated effect of AG30 in inducing mutagenesis in the *supFG1* gene of mice.

Double Patenting Rejection

Claims 6-14 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,393,376 to Peter M. Glazer. In response, enclosed is an executed Terminal Disclaimer under 37 C.F.R. 1.132, thereby overcoming the double patenting rejection.

Allowance of claims 6-14 is respectfully solicited.

Respectfully submitted,

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Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: November 15, 2002